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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,733	09/14/2001	Patrick John Thompson Vallance	117-358	9066

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EXAMINER	
PRIEBE, SCOTT DAVID	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/889,733	VALLANCE ET AL.	
	Examiner	Art Unit	
	Scott D. Priebe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *46-53,64-67 and 71-82* is/are pending in the application.

4a) Of the above claim(s) *49,64,65,67 and 79-82* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46-48,50-53,66 and 71-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 July 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/20/01, 2/26/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 46-48, 50-53 and 66 directed to human DDAHI, in the reply filed on 2/26/04 is acknowledged. The traversal is on the ground(s) that examination of all claims would not constitute an undue burden, that the claims are so linked as to form a single inventive concept because both DDAHI and DDAHII are human dimethylarginine dimethylaminohydroxylases, and that the independent claims are linking claims. This is not found persuasive. First, whether a burden of examination exists or not is not a criterion for requiring election between different inventions under PCT Rule 13.1. Second, an isolated polynucleotide encoding a human DDAH does not constitute a special technical feature or a single inventive concept, since such polynucleotides were known in the prior art (see Kimoto et al., Eur. J. Biochem. 258(2): 863-868, 1998). Finally, the determination that the inventions do not have unity of invention is not affected by the manner in which they are claimed (PCT Rule 13.3). The independent claims have been amended to recite "human dimethylarginine dimethylaminohydroxylase" rather than by listing the different SEQ ID NOs, as in the original claims. However, the specification discloses only two different human DDAH proteins, DDAHI and DDAHII.

The requirement is still deemed proper and is therefore made FINAL.

Claims 49, 64, 65, 67, and 79-82 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or

linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2/26/04.

Claim Objections

Claims 46, 47, 50-53, 66, and 71-78 are objected to because of the following informalities. Claims 46, 47, 50-53, 66, and 71-78 embrace a non-elected invention, i.e. directed to human DDAHII. Dependent claims 47, 51 and 71-78 recite "A" or "An" as the first word; these terms should be replaced with -- The -- to reflect the dependent status of the claims. Also, in claims 75 and 76, line 1, "expression" should be deleted since claim 51 is directed to "A vector". Similarly, "an expression vector" in claim 53, line 3, should be -- the vector--

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 52, 77 and 78 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 52, 77 and 78 are directed to a cell containing a polynucleotide that encodes a methylarginase. The claims recite no limitation that would exclude naturally occurring cells with an endogenous methylarginase gene, such as any cell in a human. Consequently, the claims embrace products in nature, which is non-statutory subject matter. This rejection would be overcome by amending the claims to reflect the hand of man, e.g. by claiming an isolated cell.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 46, 47, 50-53, 66, 71-78 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New Matter

Claims 46, 50, 52, and 66 have each been amended to generically recite "human dimethylarginine dimethylaminohydroxylase" in place of a listing of species of polynucleotides that included polynucleotides encoding two different human DDAH isoforms encoded by different genes. Applicant has not indicated where or how the original specification supports this generic language, as in Applicant's burden. See MPEP 714.02, last sentence of the third paragraph from the end and 2163.06 (I) last sentence. The original specification does not contain the phrase "human dimethylarginine dimethylaminohydroxylase" nor does it discuss, either implicitly or explicitly, a genus of "human dimethylarginine dimethylaminohydroxylase" as being the invention. Where human DDAHs are discussed, reference is only made specifically to

DDAHI and DDAHII. The generic terminology directs the claimed invention to polynucleotides encoding not only to DDAHI and DDAHII disclosed in the specification, but also to other human DDAH isoforms other than DDAHI and DDAHII. There is no evidence of record that Applicant had contemplated such a genus nor had possessed such a genus.

Inadequate original written description.

The claims are directed, at least in parts (a)(3), (a)(4) and (b), to a genus of polynucleotide that encodes a generic methylarginase or a sequence complementary to the polynucleotide, where the polynucleotide "hybridizes selectively to the complement of a sequence" encoding a human DDAHI or fragment of a human DDAHI. Neither the polynucleotide nor the methylarginase it encodes need be found in or isolated from a natural source, i.e. they may be completely artificial. The specification does not describe what amino acid sequence would be necessary and sufficient to provide methylarginase activity in either a natural or synthetic methylarginase. The original specification does not contain written description of such a generic polynucleotide that is adequate to demonstrate to one of skill in the art that Applicant was in possession of such a genus.

The specification (page 8, line 28 to page 9, line 1) indicates that "selective hybridization" requires at minimum only that hybridization under low stringency conditions be significantly above background. As disclosed in Kennel et al. (Progr. Nucl. Acid Res. Mol. Biol. 11: 259-301, 1971, at page 261), the minimum size of a stable heteroduplex in DNA hybridization is only 10-20 nucleotides, depending G+C content. For hybridization under high stringency conditions, only 25-50 nucleotides of complementary heteroduplex is required. SEQ ID NO: 1, encoding human DDAHI, is 858 nucleotides in length and encodes a 285 amino acid

protein. To meet the claim limitation, the hybridizing sequence encoding a methylarginase need contain only a 10-20 nucleotide sequence in common with SEQ ID NO: 1, which would need encode only 3-6 contiguous amino acids out of the 285 amino acids of SEQ ID NO: 2. Therefore, the claim language in part (a)(3) (and thereby parts (a)(4) and (b)) permits the generic polynucleotide to encode a generic methylarginase that has tremendous structural variation from that of human DDAHI, and also functional difference from a human DDAHI, since the shared coding sequence need not encode any part of the polypeptide involved directly with enzymatic activity, e.g. the active site. In essence, the claims are directed to a polynucleotide only limited by the function of the polypeptide encoded.

The court and the Board have repeatedly held (Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,18 USPQ2d 1016 (CA FC, 1991); Fiers v. Revel, 25 USPQ2d 1601 (CA FC 1993); Fiddes v. Baird, 30 USPQ2d 1481 (BPAI 1993) and Regents of the Univ. Calif. v. Eli Lilly & Co., 43 USPQ2d 1398 (CA FC, 1997)) that an adequate written description of a nucleic acid requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it, irrespective of the complexity or simplicity of the method; what is required is a description of the nucleic acid itself. It is not sufficient to define DNA solely by its principal biological property, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA with that biological property. Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. When one is unable to envision the detailed constitution of a complex chemical compound having a particular function, such as a nucleic acid, so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been

achieved until reduction to practice has occurred, i.e., until after the nucleic acid has been isolated. Thus, claiming all DNA's that achieve a result without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. That is the case here. The claims require there to be very little structural relationship between methylarginase encoded by the claimed polynucleotide and the disclosed human DDAHI.

Claim 66 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim is directed to a pharmaceutical composition comprising a polynucleotide encoding methylarginase. Recitation of "pharmaceutical composition" is a limitation of intended use, which one of skill in the art would recognize as being a use for the treatment or diagnosis of a disease in which the composition was administered to a patient. The specification (page 27) teaches generally that the claimed composition *inter alia* is to be used to treat conditions in which reduced NO production is implicated, such as hyperlipidemia, renal failure, hypertension, restenosis after angioplasty, complications of heart failure, atherosclerosis, schizophrenia, multiple sclerosis or cancer. The disclosed use of the claimed pharmaceutical composition falls into the area of gene therapy.

The prior art of record provides no evidence that polynucleotides encoding a methylarginase had been administered to an animal to study the effect of such a procedure, much

less for the treatment of a disease. The guidance in the specification for using the claimed invention in gene therapy is extremely limited (pages 29-31). It provides a general listing of the types of vectors that may be used to deliver the polynucleotide, promoters that might be used and dosages. There is no guidance specific for treating any particular disease, and no indication of where the vectors should be administered or what result an effective treatment would produce. The specification provides no working examples of a pharmaceutical composition useful for gene therapy and no working examples of such therapy. The specification fails to identify model systems in which such therapy might be developed. Thus, the specification leaves it up to one of skill in the art to determine for themselves how to use the claimed invention in therapy. The law under §112, first para. requires that the disclosure in the application shall inform those skilled in the art how to use the invention, not how to find out for themselves how to use it. In re Gardner, 166 USPQ 138, 141 (CCPA 1970). Similar to the situations in *In re Glass*, 181 USPQ 31, 35 (CCPA 1974) and *Ex parte Sudilovsky*, 21 USPQ2d 1702, 1705 (BPAI 1991), the strong feeling one gets from reading the entire specification is that either Applicant did not have possession of the details of a single operative process or, if he did, he chose not to divulge them.

At the time the invention was made was highly unpredictable and largely undeveloped art, despite high skill in the art and extensive experimentation over more than a decade. Orkin et al. reviews the state of the art of gene therapy before the instant invention was made. The overall conclusions were: 1) gene therapy for each disease would present its own scientific and clinical challenges; 2) no successful gene therapy protocol was known; 3) significant problems remained in all aspects of gene therapy, especially with respect to effective expression vectors; 4) the pathophysiology of diseases to be treated were poorly understood; 5) one cannot predictably

extrapolate the result of one animal model, such as mouse, to treatment of a disease in a different animal, such as human; 6) assessment of known gene therapy protocols was hindered by poor gene transfer, reliance on qualitative, rather than quantitative assessments of gene transfer, lack of suitable controls and poor definition of biochemical or disease endpoints; and 7) that gene therapy has been oversold, and the impression that gene therapy is successful is mistaken (pages 1-2). Each of the defects in the gene therapy art as a whole cited by Orkin et al. applies to the instant invention. Verma et al. (Nature 389: 239-242, 1997) reiterates the finding in Orkin that not a single successful gene therapy protocol has been described in the art and that lack of efficient gene delivery and sustained expression remained the Achilles heel of gene therapy (see page 239). The instant specification does not correct the deficiencies in the prior art regarding gene therapy. Rather, the specification relies upon the prior art for teaching expression constructs and nucleic acid vectors which have been tried, and some untried, which have not been successful in light of Orkin and Verma. Contrary to the assertion in the specification at page 31, lines 1-3, the prior art indicates that "a skilled physician" would not "be able to determine readily the optimum route of administration and dosage for any particular patient and condition." Verma clearly discloses that serious problems existed in this art such that no unequivocal success had been obtained for the treatment of any disease. Verma reports optimism that the problems would be surmounted and that gene therapy would one day be routine, however, there is no evidence of record that it was routine at the time the invention was made, quite the contrary. Orkin clearly makes the point that artisans in the field of gene therapy were overly optimistic and had oversold gene therapy. Rosenberg et al. (Science 287 : 1751, 2000) reported that at the time the instant application was filed, there was still no unequivocal instance of clinical efficacy with gene

therapy, and that those in the field were still guilty of overselling gene therapy, despite a decade of failure. The instant specification does not address any of the myriad problems known to plague the gene therapy art, much less suggest how to solve them.

It has long been recognized in the chemical and biological arts that the unpredictability of a particular art area may alone provide a reasonable doubt as to the accuracy of a broad statement made in support of the enablement of a claim. *Ex parte Singh*, 17 USPQ2d 1714, 1715 (BPAI 1991), *In re Marzocchi*, 169 USPQ 367, 369-370 (CCPA 1971). As set forth in *In re Fisher,* 166 USPQ 18, 24 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Therefore, in view of the highly unpredictable nature of gene therapy, the lack of any meaningful guidance in the specification, the lack of relevant working examples in the specification, and the still largely unsuccessful nature of gene therapy in general, it clearly would have required undue experimentation to practice the claimed invention for its intended use.

This rejection would be overcome by removing reference to the intended use of the composition by deleting "pharmaceutical" from line 1.

Claim 48 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 48 recites "encodes an amino acid sequence of SEQ ID NO: 1". However,

SEQ ID NO: 1 is not an amino acid sequence. Consequently, it is unclear what "amino acid sequence of SEQ ID NO: 1" means. It is suggested that "which encodes an amino acid sequence" be replaced with -- comprising the nucleotide sequence of --.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 46-48, 50-53, 66, are 71-78 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Kimoto et al. (Eur. J. Biochem. 258(2):863-868, 1998).

Kimoto discloses an isolated DNA encoding a human DDAH (Fig. 3), comprising both the coding strand and its complement. Nucleotides 323-1180 of the disclosed nucleotide sequence differ from instant SEQ ID NO: 1 only by 4 nucleotides at positions 9, 22, 76, and 846 of SEQ ID NO: 1. The amino acid sequence encoded by the disclosed polynucleotide differs from instant SEQ ID NO: 2 by only two amino acids at positions 8 and 26 of SEQ ID NO: 2. Given the near identity of the DDAH to instant SEQ ID NO: 2, this DDAH is presumed to be an allelic variant of human DDAHI.

Kimoto also discloses an expression vector comprising the coding sequence for the DDAH, a cell comprising the vector and a method of using the cell in culture to produce the DDAH.

With respect to claim 48, if the claim is interpreted as being directed to a polynucleotide comprising SEQ ID NO: 1 or a sequence complementary thereto, a "sequence complementary thereto" need not be the full complement of SEQ ID NO: 1, e.g. a sequence complementary to 100 nucleotides of SEQ ID NO: 1 meets the limitation. The polynucleotide of Kimoto (e.g. the expression vector) comprises the complement to nucleotides 77-845 of instant SEQ ID NO: 1. The rejection of claim 48 (assuming it is amended as suggested in the rejection under 35 USC 112, 2nd para.) would be overcome by replacing "a sequence complementary thereto" to -- the full complement of SEQ ID NO: 1--.

With respect to claims 71, 73, 75, and 77, these claims are not limited to a coding sequence for SEQ ID NO: 2. Rather recitation of "the human dimethylarginine dimethylaminohydrolase has the amino acid sequence of SEQ ID NO: 2" simply narrows part (a)(1) of claim 46, on which parts (a)(2)-(4) and part (b) are based. The DNA of Kimoto meets the limitations of parts (a)(2)-(4) and (b), relative to SEQ ID NO: 2. The rejection of claims 71, 73, 75, and 77 would be overcome by limiting these claims to where the polynucleotide encodes SEQ ID NO: 2.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. GenBank Acc. No. AB001915 also discloses the nucleotide sequence and amino acid sequence for the human DDAH disclosed in Kimoto.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy J. Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Scott D. Priebe
Primary Examiner
Art Unit 1632